Applicants have noted the objections to the drawings. Applicants will submit corrected drawings.

The Examiner has objected to claims 6, 8 and 9 because they refer to non-elected species not examined on the merits. In response, Applicants have amended claim 6 to delete the reference to non-elected species. Additionally, Applicants have canceled claims 8 and 9, making the objection to these claims moot.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112

Claim 11 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claim 11 under 35 U.S.C. § 112, first paragraph, on the grounds that the "specification lacks complete deposit information for the deposit of antibodies HU177, HUVIV26 [sic "HUIV"] and XL313." Office Action at page 6. The Examiner states that it "is not clear that antibodies possessing the identical properties of these instant antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation." Id. The Examiner further states that "a suitable deposit of the molecules designated as HU177, HUIV26 and XL313 for patent purposes, evidence of public availability of the claimed cell lines or evidence of the reproducibility without undue experimentation of the claimed cell lines, is required." Id. at page 7.

Pursuant to 37 CFR § 1.809(b)(2), Applicants respectfully disagree. A deposit is not required under the circumstances of the application. The Examiner states that the "specification lacks complete deposit information for the deposit of antibodies HU177, HUVIV26 [sic "HUIV26"] and XL313. It is not clear that antibodies possessing the identical properties of these instant antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation." Office Action, page 6.

Under 37 CFR § 1.801, biological material that must be deposited is "material that is capable of self-replication either directly or indirectly." Although, the source hybridomas for the referenced antibodies may constitute depositable material, the antibodies themselves constitute nonreproductive material and, as such, should not be covered by the deposit rules. Therefore, Applicants respectfully request that this rejection be withdrawn.

Claims 1-4 and 6-18 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1-4 and 6-18 under 35 U.S.C. § 112, first paragraph on the grounds that the specification "does not reasonably provide enablement for a host of antagonists, such as an oligonucleotide." Office Action, page 8.

Applicants submit that they have provided sufficient guidance and working examples to enable the claimed invention. Enablement requires that one of ordinary skill in the art can practice the invention without undue experimentation. In re Wright, 27 U.S.P.Q. 2d 1510, 1513 (Fed.Cir. 1993). Enablement is not precluded by the necessity for some experimentation – the key word is undue and not experimentation. Using Applicants disclosure, a person of ordinary skill in the art can develop a host of antagonists as claimed with some routine experimentation.

The specification provides that the antagonists of the invention are such that they recognize cryptic epitopes in collagens, such as collagen type-I. Such antagonists would bind to denatured collagens with much greater affinity than to native collagens because denaturation exposes cryptic epitopes. Thus, an identification of cryptic epitopes in a collagen would provide a basis for developing a host of antagonists that would bind to that epitope. A person of ordinary skill in the art, then, can, with some routine screening, select from such antagonists the antagonists of the invention, i.e., antagonists that have a relatively low affinity for the native triple helical form of the collagen. Indeed, the specification provides examples of screening of monoclonal antibody libraries for antagonists of denatured collagen to identify not one but three monoclonal antibodies that inhibit angiogenesis, a fact acknowledged by the Examiner. Office Action at page 8. Similarly, screening of other libraries of potential antagonists is well within the capabilities of a person of ordinary skill in the art.

For example, methods for synthesis and screening of oilgonucleotide combinatorial libraries are available and widely used to identify oligonucleotide antagonists of a

desired form of a target molecule. See Jellinek et al.[1], *Biochemistry*, 33(34):10450-6 (1994), which, in part, states that "[t]he proliferation of new blood vessels (angiogenesis) is a process that accompanies many pathological conditions including rheumatoid arthritis and solid tumor growth. Among angiogenic cytokines that have been identified to date, vascular endothelial growth factor (VEGF) is one of the most potent. We used SELEX [systematic evolution of ligands by exponential enrichment; Tuerk, C., & Gold, L. (1990) *Science* 249, pp. 505-510 to identify RNA ligands that bind to VEGF in a specific manner with affinities in the low nanomolar range. Ligands were selected from a starting pool of about 10(14) RNA molecules containing 30 randomized positions. Isolates from the affinity-enriched pool were grouped into six distinct families on the basis of primary and secondary structure similarities. Minimal sequence information required for high-affinity binding to VEGF is contained in 29-36-nucleotide motifs. Binding of truncated (minimal) high-affinity ligands to VEGF is competitive with that of other truncated ligands and heparin. Furthermore, truncated ligands from the six ligand families inhibit binding of [125I]VEGF to its cell-surface receptors. Oligonucleotide ligands described here represent an initial set of lead compounds in our ongoing effort toward the development of potent and specific VEGF." Also see, Ecker, et al, *Nucleic Acids Res.*, 21(8):1853-6 (1993), which provides that "[c]ombinatorial strategies offer the potential to generate and screen extremely large numbers of compounds and to identify individual molecules with a desired binding specificity or pharmacological activity. We describe a combinatorial strategy for oligonucleotides in which the library is generated and screened without using enzymes. Freedom from enzymes enables the use of oligonucleotide analogues. This dramatically extends the scope of both the compounds and the targets that may be screened. We demonstrate the utility of the method by screening 2'-O-Methyl and phosphorothioate oligonucleotide analogue libraries. Compounds have been identified that bind to the activated H-ras mRNA and that have potent antiviral activity against the human herpes simplex virus."

Thus, Jellinek et al. and Ecker et al. teach that high throughput screens are available for screening for oligonucleotide antagonists of molecules including protein.

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[1] References cited in this response are included in the Information Disclosure Statement filed concurrently herewith.

Furthermore, Applicants' antibodies HUI77, HUIV26, and Xl313 define three distinct epitopes. Antibody HUI77 blocks migration of cells and blocks the ability of a subset of purified integrin molecules from binding to purified denatured type-I collagen. Antibody XL313 blocks the ability of a subset of purified integrin molecules from binding to purified denatured type-I collagen. Because the mechanism of the action of the antibodies HUI77 and XL313 involves sterically blocking the interaction of certain integrins with collagen sequences defined by the epitope of these antibodies it is obvious that other molecules that bind to the same epitope will very likely block these integrin interactions with collagen and angiogenesis. These epitopes in denatured type-I collagen when isolated as small peptides could, by one skilled in the art, readily be used to identify oligonucleotides in a combinatorial library that bind with high affinity to these defined epitopes. Then, the isolated antagonists could readily be tested for inhibition of angiogenesis. Oligonucleotide antagonists of the epitopes in denatured type-I collagen defined by Applicants' antibodies HUI77 and XL313 are likely to also inhibit angiogenesis.

Additionally, high throughput screening methods of complex libraries of other classes of molecules are also available, such as phage-peptide libraries for screening of peptide antagonists and libraries of synthetic organic molecules.

The Examiner asserts that Applicants' "enabling disclosure [for HUI77, HUIV26, and XL313] provides evidence only of the specified antagonists capable of arresting angiogenesis. Applicants have not provided any evidence that suggests that other monoclonal antibodies or oligonucleotides would have the same inhibitory effect." Office Action at page 8. This assertion is unwarranted.

The Application teaches generalized methods for identification of antagonists of novel epitopes in denatured collagen that block angiogenesis and are amenable to high-throughput screening by one skilled in the art. For example, the method used for the isolation of HUI77 is easily generalized:

- First antagonists of denatured type-I collagen that do not bind well to native collagen are screened by a simple binding assay that is amenable to high throughput screening.

- Second, the isolated antagonists are screened for antagonists that block cell adhesion in a method amenable to high throughput screening. Also the denatured type-I collagen antagonists are screened for antagonists that block cell migration in a method amenable to high throughput screening. Also, the antagonists can be readily tested for the ability to block the binding of certain integrins to denatured collagens.

- Third, those unique antagonists that either affect cell adhesion or migration or integrin/collagen interactions can be tested in standard angiogenesis assays.

The first two steps of the high throughput screening procedure are expected to identify a small subset of molecules from the complex library that meet the criteria of the first two steps in a screen. Therefore, contrary to the Examiner's assertion, testing of these molecules for anti-angiogenic activity is not expected to be burdensome.

It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. All that is needed is that the disclosure, either through illustrative examples or terminology, adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. In re Vaeck, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991).

Claims 1-4 and 6-18 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-4 and 6-18 under 35 U.S.C. § 112, second paragraph on the grounds that the "recitation 'denatured collagens' in claims 1 and 6-9 is vague and indefinite." Applicants respectfully traverse the rejection. The Examiner's attention is drawn to the following section of the specification discussing "denatured collagens":

> Denatured collagen refers to collagen that has been treated such that it no longer predominantly assumes the native triple helical form. Denaturation can be accomplished by heating the collagen. In one embodiment, collagen is denatured by heating for about 15 minutes to about 100 ° C. Denaturation can also be accomplished by treating the collagen with a chaotropic agent. Suitable chaotropic agents include, for example, guanidinium salts. Denaturation of a

> collagen can be monitored, for example, by spectroscopic changes in optical properties such as absorbance, circular dichroism or fluorescence of the protein, by nuclear magnetic resonance, by Raman spectroscopy, or by any other suitable technique. Denatured collagen refers to denatured full length collagens as well as to fragments of collagen. A fragment of collagen can be any collagen sequence shorter than a native collagen sequences. For fragments of collagen with substantial native structure, denaturation can be effected as for a native full-length collagen. Fragments also can be of a size such that they do not possess significant native structure or possess regions without significant native structure of the native triple helical form. Such fragments are denatured all or in part without requiring the use of heat or of a chaotropic agent. The term denatured collagen encompasses proteolyzed collagen. Proteolyzed collagen refers to a collagen that has been fragmented through the action of a proteolytic enzyme. In particular, proteolyzed collagen can be prepared by treating the collagen with a metalloproteinase, such as MMP-1, MMP-2 or MMP-9, or by treating the collagen with a cellular extract containing collagen degrading activity or is that which occurs naturally at sites of neovascularization in a tissue.

Specification page 14, line 27 to page 15, line 17.

In view of the above, the Examiner's rejection of claims 1-4 and 6-18 under section 112, second paragraph for recitation of "denatured collagen" is clearly untenable. Applicants, therefore, request that the rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-4, 6-8, 10 and 12-14 Over Bellon

The Examiner rejected claims 1-4, 6-8, 10 and 12-14 under 35 U.S.C. § 103(a) as being unpatentable over Bellon. Applicants respectfully disagree. Bellon is directed to detection and quantification of collagenous proteins within cynogen bromide (CNBr) digested tissue samples. However, it is not concerned with angiogenesis and certainly not with Applicants' antagonists for inhibiting angiogenesis. Thus, as such, Bellon is inapplicable to Applicants' invention.

While Bellon discloses antibodies that bind to collagen type-I, collagen type-III, collagen type-IV or collagen type-V obtained from CNBr digested tissue, Bellon contains no suggestion whatsoever of an antagonist as set forth in claim 1 of the instant application. Claim 1 recites an

antagonist that specifically binds to a denatured collagen or collagens but binds to the native triple helical form of each of said collagens with substantially reduced affinity and wherein said antagonist inhibits angiogenesis.

Claim 1 (emphasis added). Far from disclosing antagonists that bind to the native triple helical form of collagen type-I with substantially reduced affinity compared to the affinity for denatured collagen type-I, Bellon does not even once mention the native triple helical form of collagen type-I, or of any other collagen for that matter. Thus, to suggest that antagonists as claimed by Applicants are obvious in view of Bellon strains credulity.

The Examiner's reasoning that Bellon teaches antibodies that bind to denatured collagen type-I but bind to the native triple helical form with substantially reduced affinity is flawed at its core. The Examiner first asserts that Bellon discloses both monoclonal and polyclonal antibodies that bind denatured collagenous proteiens. Office Action, page 10. The Examiner, then, takes the statement in Bellon that ELISA cannot be used on whole tissue samples because of the insolubility of the collagens to conclude that the antibodies disclosed in Bellon "would bind the native triple helical form of the collagen type I with substantially reduced affinity, from 3 fold lower to 10 fold lower than that for denatured collagen." Id.

Applicants respectfully submit that the Examiner's conclusion is unfounded and unacceptable. All that Bellon asserts is that the insolubility of collagens makes ELISA unusable. Bellon makes no mention of ELISA not being usable because the antibodies do not bind to the native triple helical form.

The Examiner asserts that the whole tissue samples invariably contain native triple helical forms of collagen type-I. From there the Examiner reasons that because ELISA does not work with whole tissue samples, Bellon's antibodies will not bind with the native triple helical form of collagen type-I. But, according to Bellon, that's clearly not the reason why ELISA does not work. According to Bellon ELISA does not work because of the insolubility of collagens. Dissolution of collagens has nothing to do with the comparative affinity of Bellon's antibodies for denatured collagen type-I versus the native triple helical form of collagen type-I. If anything, Bellon's observation that collagens in whole tissue samples are insoluble implies that Bellon did not even have the opportunity to test the binding affinity of his antibodies to the

native triple helical form of collagen type-I. Clearly, the Examiner is reading into Bellon an element of claim 1 that is simply not there. This is impermissible.

The Examiner appears to believe that Bellon's antibodies have an intrinsic quality of binding to "the native triple helical form of the collagen type I with substantially reduced affinity, from 3 fold lower to 10 fold lower than that for denatured collagen." Id. However, the Examiner provides no basis as to why Bellon's antibodies have the purported intrinsic quality. In accordance with Applicants' invention, an antagonist of denatured collagen will bind to the native triple helical form with much less affinity, if the antagonist is directed to a cryptic epitope. Therefore, the Examiner's belief appears to rest on the unfounded assumption that epitopes found in CNBr fragments of collagen (presumably denatured collagen) that are recognized by an antisera must be cryptic epitopes, not recognizable in a triple-helical conformation. Certainly, in the general case, it is easy to envision an epitope defined by a contiguous peptide sequence that is exposed on the surface of native collagen and that is recognized by an antibody whether the collagen is native or denatured. There is simply no basis to assume that because a polyclonal antisera can react with a CNBr fragment, it is somehow devoid of reactivity towards native collagen.

In fact, the polyclonal antibodies[2] described in Bellon cannot have the purported quality. In general, the native triple helical form of a collagen is far more immunogenic than its denatured form. See, for example, Timpl, *Methods in Enzymology*, 82 Pt A:472-98 (1982) at page 473 ("Compared to native triple-helical collagen, the denatured, unfolded products are very often weaker immunogens or may be inactive in animal species that mainly respond against helical antigenic determinants.") Therefore, a person of ordinary skill in the art will expect that common antibodies to collagen, such as those described in Bellon, will bind to the native triple helical form with much greater specificity than to the denatured form.

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[2] Note that Bellon only refers to polyclonal antisera raised in rabbits and not monoclonal antibodies as suggested by the Examiner. Office Action at page 10.

For additional proof of this, one need look no further than Bellon. Bellon cites Wick et al.[3] for the method of generating antibodies by immunizing with pepsin extracted collagen. This method, by its very nature, yields native collagen because denatured collagen is reduced to peptides by pepsin. Therefore, the anti-collagen antisera of Wick et al. can indeed react with native collagens. Consequently, in sharp contrast to the Examiner's conclusion, Bellon's antibodies will likely have a greater affinity for the native triple helical form of collagen type-I than for denatured collagen type-I, implying that Bellon teaches directly away from Applicants invention.

At a fundamental level, too, the antagonists of the invention can be distinguished over common antibodies to collagen, such as those of Bellon. The antagonists of the present invention are directed to cryptic epitopes in collagens. Such epitopes are not exposed for recognition in the native triple helical form of collagens – they are only exposed upon denaturation of collagens. See Specification at page 15, ll. 18-24. Therefore, the antibodies claimed in the application, unlike those referenced in Bellon, bind to the native triple helical form of a collagen with much less specificity than to its denatured form because denaturation exposes the cryptic epitopes. It is also worth noting that because the antibodies of the invention recognize cryptic epitopes, special techniques must be used to obtain them. See, for example, Example I in the Specification at pages 37-38.

Furthermore, the antibodies described in Bellon do not inhibit angiogenesis, as claimed in claim 1. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royko, 490 F.2d 981 (CCPA 1974). Applicants' claimed antagonists inhibit angiogenesis. Bellon, on the other hand, is not even concerned with inhibition of angiogenesis. Bellon is disclosing the use of off-the-shelf antibodies to collagenous proteins to detect and quantify collagenous proteins obtained from

[3] Wick, G., Glanville, R.W., and Timpl, R., *Immunobiology*, 156(4-5):372-81 (1980)

CNBr digested tissue.[4] Far from disclosing antagonists or antibodies that can inhibit angiogenesis, Bellon does not once mention angiogenesis.

The Examiner states that it would have been "*prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the antibodies of Bellon to a subject with angiogenesis. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Bellon. As suggested on page 201, column 1 the technique taught has a number of potential uses such as detection and quantification of collagens in a number of diseases. Those antibodies used in Bellon's method could also be considered therapeutic in the inhibition of angiogenesis." Office Action at pp. 4-5 .

Thus, the Examiner seizes upon an unsupported, solitary statement in Bellon to reach the conclusion that Bellon's antibodies can be considered to be therapeutic in the inhibition of angiogenesis. Such a conclusion is unwarranted because Bellon contains absolutely no enabling disclosure showing the use of his antibodies to inhibit angiogenesis. In fact, far from showing the use of his antibodies to inhibit angiogenesis or treat any disease, Bellon does not even contain an enabling disclosure to show that his antibodies could be used to detect angiogenesis, or any disease, for that matter. Mere speculation that the antibodies potentially could be used to detect or quantify collagens in a disease cannot be the basis for rejecting Applicants' antagonists that inhibit angiogenesis.

The Examiner is impermissibly modifying Bellon to assert that the antibodies described in Bellon would inhibit angiogenesis. There is no suggestion in Bellon to support the Examiner's assertion. " Modification unwarranted by the disclosure of a reference is improper." Carl Schenck, A.G. v. Nortron Corp., 218 U.S.P.Q. 698, 703 (Fed. Cir. 1983). The M.P.E.P.

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[4] It is worth noting that Bellon does not teach the quantification of denatured collagen in a tissue, an increase of which would be a marker of increased MMP activity that is associated with angiogenesis and tumor invasion. Bellon requires that the tissue first be digested with CNBr which results in digestion and denaturation of the native collagen as well as the digestion of denatured collagen in tissue. Thus, Bellon does not seek to determine the amount of collagen that is denatured in a tissue but rather total collagen composition of the tissue.

states that "[o]bviousness can only be established by . . . modifying the teaching of the prior art to produce the claimed invention where there is some teaching, suggestion , or motivation to do so found either in either the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. § 2143.01, 2100-98 (February 2000). The Examiner does not point to any discernible suggestion in Bellon for the proposed modification.

The Federal Circuit has stated that it is impermissible simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. Interconnect Planning Corporation v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985). For all of the foregoing reasons, Applicants submit that the attempted modification of Bellon is based on impermissible hindsight reconstruction and the cited reference does not provide any teaching that would have rendered Applicant's claim 1 obvious.

Claims 1-4, 6-8, 10, 12-14, 16 and 17 Over Bellon In View Of US Patent No. 5,693,762 (the "'762 Patent")

Applicants respectfully submit that this claim rejection is improper. Bellon has been discussed *supra*. The '762 Patent, if at all relevant, can only be relevant to dependent claim 16 because the Examiner only cites it for teaching the method of humanizing antibodies and fragments of immunoglobulins. The '762 Patent has no relevance to the other claims. Moreover, even as to claim 16, the rejection is improper because, as discussed above, Bellon does not even disclose the non-humanized antagonists of the invention. Further, there is no suggestion in either Bellon or the '762 Patent to combine the teachings of Bellon with the '762 Patent. Therefore, combining Bellon with the '762 Patent is improper and, in any case, the combination does not provide the claimed invention because Bellon does not disclose the claimed antagonists.

The U.S. Court of Appeals for the Federal Circuit has held that "[t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness...It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The Examiner does not point to any discernible suggestion in either Bellon or the '762 Patent that would lead one of ordinary skill in the art to combine the two references. What the Examiner offers is the unsupported assertion that a skilled artisan would have been motivated to combine the two references.

Such an assertion cannot be used to base a finding of obviousness. Id. The In re Fine court held that "the Examiner's bald assertion" that substitution of an element from one reference into another "would have been within the skill of the art" cannot support a finding of obviousness. Id. In the instant case too, the Examiner's statement about combining Bellon with the '762 Patent is an assertion that is not adequate to support a 103 rejection of Applicant's pending claims.

Claims 1-4, 6-8, 10, 12-14, 16 and 17 Over Bellon In View Of European Patent 0 510 949 A2 (the "'949 Patent")

As with the preceding rejection, Applicants respectfully submit that this claim rejection is improper. Bellon has been discussed *supra*. The '949 Patent, if at all relevant, can only be relevant to dependent claim 18 because the Examiner only cites it for teaching the method of preparing antibody-cytokine fusion protein moieties for use in immunotherapeutic treatment methods. The '949 Patent is not relevant to the other claims. Moreover, even as to claim 18, the rejection is improper because, as discussed above, Bellon does not even disclose the antagonists of the invention that are not conjugated to cytotoxic or cytostatic agents. Further, there is no suggestion in either Bellon or the '949 Patent to combine the teachings of Bellon with the '949 Patent. See *supra*, for arguments against combining references. Therefore, combining Bellon with the '949 Patent is improper and, in any case, the combination does not provide the claimed invention because Bellon does not disclose the claimed antagonists.

If an independent claim is nonobvious under 35 U.S.C. § 103, any claim dependent thereon is nonobvious. In re Fine, 837 F.2d at 1076. As the foregoing shows, Bellon, alone or in combination with any other reference, does not make independent claim 1 obvious. Therefore, claims 2-4 and 6-18 that are dependent on claim 1 are also nonobvious.

FEE DUE TO FILE THIS AMENDMENT

No fee is due to file this amendment and response.